SYNTHESIS OF BENZENESULFONAMIDE-BEARING AZOLE DERIVATIVES AS HUMAN CARBONIC ANHYDRASE INHIBITORS

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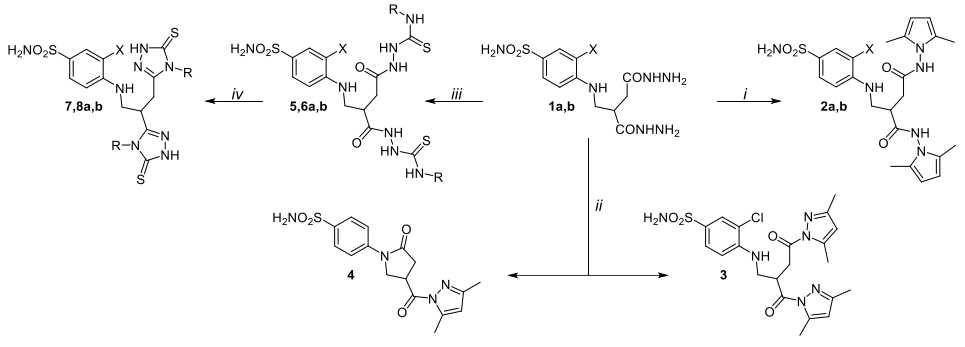
Reversible hydration of CO_2 to protons and bicarbonate is catalyzed by twelve alpha carbonic anhydrase (CA) isozymes found in human body. This is a crucial reaction for the respiratory processes and CO_2 transport between tissues, in pH regulation and homeostasis [1]. Increased expression levels of several CA isozymes are associated with many diseases. CAs are established therapeutic targets of cancer (CA IX and CA XII), glaucoma (CA II, CA IV, CA XII) and obesity (CA VA and CA VB). Currently, most of the research is focused on designing and developing inhibitors against CA IX that show potential for treating solid tumors [2].

Pyrroles **2a,b** were obtained from hydrazides **1a,b** by their reactions with hexane-2,5-dione in propan-2-ol at reflux (Scheme 1). Furthermore, there was an attempt to synthesize 3,5-dimethylpyrrazoles using the same method. Unfortunately, only one of desired products (compound **3**) was obtained. In attempt to synthesize non-chlorinated analogue of compound **3**, pyrazole **4** was isolated from reaction mixture. It was suggested, that due to acidic properties of pentane-2,4-dione, 2-pyrrolidone ring closure had occurred during the reaction. However, it is suspected that some steric hindrance, which occurs due to chlorine substitute at C-2 of phenyl ring, prevents the closure of 2-pyrrolidone ring during synthesis of compound **3**. Furthermore, reactions of hydrazides **1a,b** with corresponding methyl or phenyl isothiocyanate in DMF led to the formation of carbothioamides **5,6a,b**, which were further cyclized into triazoles **7,8a,b**.



a: X = H; **b: X =** Cl;
5: R = CH_3; **6:** R = C_6H_5; **7:** R = CH_3; **8:** R = C_6H_5;

Reaction conditions: *i*) hexane-2,5-dione, propan-2-ol, reflux, 5 h; *ii*) pentane-2,4-dione, reflux, 5h; *iii*) corresponding isothiocyanate, DMF, r.t., 4-6 h; *iv*) 2% KOH, r.t., 8 h;

Scheme 1. Synthesis of benzensulfonamide-bearing azole derivatives.

The structures of all synthesized compounds have been confirmed by the data of ^{1}H and ^{13}C NMR, FT-IR spectroscopy as well as mass spectrometry data. Compound binding to human CA isoforms was measured by fluorescent thermal shift assay. The compounds bound CAs with submicromolar affinity.

References

1. Aggarwal, M., et al. J. Enzyme Inhib. Med. Chem. 2013, **28**, 267–277.
2. R. G. Gieling, et al. Bioorg. Med. Chem. 2019, **21**, 1470–1476.